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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/301,704	04/29/1999	MARK ANDREW SCHEMBRI	54259.000003	5964

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EXAMINER

SHEINBERG, MONIKA B

ART UNIT PAPER NUMBER

1634

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/301,704	SCHEMBRI ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Monika B Sheinberg	1634	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10/03/2002.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) 16,17 and 26-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-10,12-15 and 18-25 is/are rejected.
- 7) ☒ Claim(s) 5 and 11 is/are objected to.
- 8) ☒ Claim(s) 1-32 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

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**DETAILED ACTION**

***Response to Arguments mailed 03 October 2002***

Applicants' arguments, filed 03 October 2002, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicants are reminded that claims 16, 17 and 26-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in response received 16 August 2001.

Claims 1-15 and 18-25 have been examined.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 8, 9, 12-15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Pallesen et al. (*Microbio.*, 1995).

Pallesen et al. describes a method of engineering a chimeric FimH adhesin on the surface of a gram negative bacterium, *Enterobacteriaceae* species (*Escherichia coli*), by way of peptide insertion into the extracellular domain to create new binding domains "without affecting compatibility with the [...] adhesive ability" (p. 2840, 2<sup>nd</sup> column, 2<sup>nd</sup> paragraph) as recited by claims 1-4 and 12-14. The non-naturally occurring binding region (claim 6) that binds to that which the intrinsic region would not is that of that of the preS2 sector of the hepatitis B surface antigen and epitope from cholera toxin" (p. 2840, 2<sup>nd</sup> column, 2<sup>nd</sup> paragraph); the cholera toxin

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subunit being of 50-64 amino acids (p. 2841, 1st column, 1st paragraph) as required by claim 8. Figure 3 (p. 2842) demonstrates the requirement of at least one histidine residue (claim 9) in addition to the preS2 region being made up of less than 100 amino acids. Figure 1 (p. 2840) displays the plasmids utilized with the corresponding heterologous inserts. The population of recombinant cells recited in claim 18 are inherent to the method of generating the method described by Pallesen et al. (p. 2840, methods).

Examiner would like to note that although Pallesen et al. may report results of reduced adhesiveness, the instant claims only require two domains to be available, one potentially modified intrinsic site and the other non-natural. The affinity of the intrinsic binding region is not called into question by the instant claims (aside from claim 5). Even so, a reduced adhesiveness can also be interpreted to be within the parameters of a modified natural binding region. As such, the chimeric FimH produced by the reference remains encompassed by the claims. Applicants argue that Pallesen et al. does not teach co-existing binding sites, the first as an optionally modified intrinsic binding site and the second non-naturally occurring. However this is not persuasive because Pallesen et al. does teach co-existing binding sites in that heterologous sequences were inserted and show to be in "immunologically active forms on the surface of the chimeric FimH adhesin" without disturbing or altering the intrinsic adhesive ability, or natural binding site on the adhesin.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-10, 12-15 and 18-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pallesen et al. (*Microbio.*, 1995) as applied to claims 1-4, 6, 8, 9, 12-15 and 18 above, and in view of Sousa et al. (*Proc. Natl. Acad. Sci.*, 1992) and Georgiou et al. (*Nat. Biotech.*, 1997).

Pallesen et al. describes a method of engineering a chimeric FimH adhesin on the surface of a gram negative bacterium, *Enterobacteriaceae* species (*Escherichia coli*), by way of peptide insertion into the extracellular domain to create new binding domains "without affecting compatibility with the [...] adhesive ability" (p. 2840, 2<sup>nd</sup> column, 2<sup>nd</sup> paragraph) as recited by claims 1-4 and 12-14. The non-naturally occurring binding region (claim 6) that binds to that which the intrinsic region would not is that of that of the preS2 sector of the hepatitis B surface antigen and epitope from cholera toxin" (p. 2840, 2<sup>nd</sup> column, 2<sup>nd</sup> paragraph); the cholera toxin subunit being of 50-64 amino acids (p. 2841, 1st column, 1st paragraph) as required by claim 8. Figure 3 (p. 2842) demonstrates the requirement of at least one histidine residue (claim 9) in addition to the preS2 region being made up of less than 100 amino acids. Figure 1 (p. 2840) displays the plasmids utilized with the corresponding heterologous inserts.

Applicants argue that Pallesen et al. actually reports results of reduced adhesiveness, however the instant claims only require two domains to be available, one potentially modified intrinsic site and the other non-natural. As such, the chimeric FimH produced by the reference remains encompassed by the claims. Applicants argue that Pallesen et al. does not teach co-existing binding sites, the first as an optionally modified intrinsic binding site and the second non-naturally occurring. However this not persuasive because Pallesen et al. does teach co-existing binding sites in that heterologous sequences were inserted and show to be in "immunologically active forms on the surface of the chimeric FimH adhesin" without disturbing or altering the intrinsic adhesive ability, or natural binding site on the adhesin.

Pallesen et al. does not teach the clone library requirements of claims 19-25.

Georgiou et al. teaches the use of heterologous proteins exposed on the surface of microorganisms as a useful tool in creating combinatorial libraries to screen recombinant

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vaccines (abstract). The reference also teaches the display of such heterologous proteins on “[e]xtracellular proteinaceous appendages like pili and flagella” (p. 29 , 2<sup>nd</sup> column, 1<sup>st</sup> paragraph) of gram negative *Enterobacateriaceae* species (*E.coli*)

Pallesen et al. does not teach the methallobinding modification of claims 7 and 10.

Sousa et al. suggests the use of “flagellar proteins of gram-negative bacteria as anchor sites for peptides” (p. 1017, 1<sup>st</sup> column, 1<sup>st</sup> paragraph) in the engineering of bacterial cells to have increase metal binding affinity, although demonstrated on a non-fimbrial protein. The enrichment of the cell population containing these Ni compound binding heterologous proteins is suggested by the use of the adhesions to beads described on page 1019 (2<sup>nd</sup> column, 4<sup>th</sup> paragraph). Although the LamB protein is not a fimbrial adhesin, Sousa et al. motivates the modification of bacterial surface proteins to include higher metal binding affinities by it advantages of targeting toxic metals (p. 1019, 1<sup>st</sup> column, 4<sup>th</sup> paragraph).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to perform the production of a cell containing the chimeric FimH adhesin of Pallesen et al. and further modify the non-natural or second kind of binding region to include increased metal-binding affinity using the Histidine clusters as per Sousa et al. It would have been further obvious to perform the cell production method of Pallesen et al. in view of Sousa et al. to include a larger population of the generated recombinant cells as a library as per Georgiou et al. for purposes of screening live recombinant vaccines.

### ***Claim Objections***

Claims 5 and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### ***Conclusion***

Claims 1-4, 6, 8, 9, 12-15 and 18 are rejected under 35 U.S.C. 102(b). Claims 1-4, 6-10, 12-15 and 18-25 are rejected under 35 U.S.C. 103(a). Claims 5 and 11 are objected to as being dependent upon a rejected base claim. As such, no claim is allowed.

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*Inquiries*

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 308-4242.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Monika B. Sheinberg, whose telephone number is (703) 306-0511. The examiner can normally be reached on Monday-Friday from 1 P.M to 8 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

April 7, 2003

Monika B. Sheinberg  
Art Unit 1634

*MBS*

  
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